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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/297,486	06/14/1999	JOHN FRANCIS MARTIN	GJE-30	9834

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/297,486	MARTIN ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,9 and 39-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,9 and 39-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/22/1999*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 11/8/05.

Claims 1-6, 8, 9 and 39-42 are pending and under consideration in this Office Action.

Information Disclosure Statement

Attached please find a corrected version of the information disclosure statement filed 7/22/99. The Urquhart reference (US Patent 3,797,485) was inadvertently not initialed on the copy previously sent to Applicant on 6/25/03. This oversight is corrected on the attached copy.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8, 9 and 39-42 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting intimal hyperplasia at a site in a blood vessel in a rabbit, by periadventitial administration at the site of a DNA expression vector encoding vascular endothelial growth factor (VEGF), does not reasonably provide enablement for treatment of any vascular disorder in any species other than a rabbit. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention

commensurate in scope with these claims, for the reasons of record in Paper Nos. 15 and 18.

Claims 1-6, 8, 9, and 39-42 are drawn to methods of inhibiting or reducing intimal hyperplasia. The recited method steps require administration of a nucleic acid encoding human VEGF. The nucleic acid must be delivered periadventitially to a site where intimal hyperplasia is present or may occur. The claims require inhibition or reduction of hyperplasia. In a previous Action, the phrase "whereby intimal hyperplasia of the blood vessel is ... reduced" was interpreted as embracing reversal of existing hyperplasia. However, the specification was carefully reconsidered, and there was no evidence that Applicant wished to embrace reversal of existing hyperplasia by this phrase, but instead focused on inhibiting hyperplasia, i.e. reducing or limiting the extent limiting the extent of hyperplasia. Claims 39-42 are drawn to methods of delivery of a human VEGF protein to a cell of a blood vessel whose endothelium is intact by periadventitial administration of a nucleic acid encoding the human VEGF. The specification discloses no other purpose for performing this method than for inhibiting intimal hyperplasia for the purpose of treating or prevention of stenosis or restenosis. As a result, claims 39-42 face the same enablement issues as claims 1-6, 8, and 9.

The specification teaches a working example in which plasmid expression vectors encoding VEGF were complexed with liposomes and delivered to the adventitial surface of a rabbit carotid artery underneath a silicone collar. It was previously shown that placement of a silicone collar on a rabbit carotid artery causes intimal hyperplasia. Injection of VEGF plasmid/liposome complexes inhibited intimal hyperplasia, but this

inhibition decreased after two weeks, probably due to a loss of transient gene expression. See the specification at page 33, lines 11-22, and page 36, lines 20-26.

Nucleic acid-mediated therapy

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "[s]ignificant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host", (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) teach that "[t]here is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "[t]hus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "[t]here is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30).

With specific respect to therapies based on the transfer of VEGF to the arterial wall, Laitinen (Pharm. Res. 4744): 251-254, 4/1998) taught that although promising effects on cardiovascular diseases have been noted by adventitial delivery of genes in animal models using the collar device disclosed at page 16, lines 21-23 of the specification, "further studies regarding gene transfer techniques, vectors, and safety of procedures are needed before a full therapeutic potential of gene therapy in vascular diseases can be evaluated." See abstract. See also sentence bridging pages 252 and 253, and last sentence of CONCLUSIONS on page 253. Thus the treatment of vascular diseases in general by delivery of VEGF nucleic acids was unpredictable at the time the invention was filed.

Relevance of animal models of intimal hyperplasia to human disease and treatment

The prior art teaches that successful treatment of intimal hyperplasia in small animal models is not predictive of success in other animals, particularly in humans. Muller et al (J. Amer. Coll. Cardiol. 19(2):418-432, 1992) teach that, as of 1992, greater than 50 studies had shown that at least 9 different classes of pharmacological agents inhibit intimal proliferation in response to arterial injury in animal models. However, none of these agents reproducibly reduced the incidence of restenosis after coronary balloon angioplasty in humans. To explain these results, Muller considered the differences between the various systems. Significant interspecies and intraspecies differences were found to exist among the various animal models, particularly with respect to the extent and composition of neointimal thickening, drug and lipid

metabolism, and the activity of coagulation and fibrinolytic systems. The instant specification teaches a single example of inhibition of intimal thickening at the precise site of VEGF expression vector administration in a rabbit model of intimal hyperplasia. See Example 1, pages 33-38. The specification teaches no example of reversal of intimal hyperplasia in any model. With respect to rabbit models, Muller notes that rabbit arteries are not necessarily structurally equivalent to human arteries. For example, the amount of elastin in the media of coronary arteries is less than that in larger mammals, the intima is thinner, and the subendothelial space between the endothelium and the internal elastic lamina is very narrow and virtually acellular. A similar intimal structure is found in the arteries of humans only during fetal and early neonatal life. See paragraph bridging columns 1 and 2 on page 420. Muller teaches that these differences may account for the variability in sensitivity of various animal models to treatments, and should be considered carefully in the interpretation of experimental studies. See abstract. Also, after reviewing rat, rabbit, dog, non-human primate, and pig models Muller found that it was "clear that there are major differences among the animal models, particularly in terms of the nature of arterial injury and the composition of the neointima. It could be expected, therefore, that a pharmacological therapy that is effective in one animal model may be ineffective in another species or in humans." See page 426, column 2, first full paragraph. Thus Muller clearly indicates that results in one animal model are not necessarily predictive of results in another animal model due to physiological differences between the models.

Lafont et al (Ann. Card. Ang. 44(7): 349-353, 9/1995), reviewed the results of fifteen years of research prior to 1995, and conclude that "[a]ll the restenosis strategies based on inhibition of smooth muscle cell proliferation, which successfully limited restenosis in animal models have failed in man, due to hazardous extrapolations from experimental models which are very different from the atheromatous lesions observed in man". See abstract. Lafont et al (Card. Res. 39(1): 50-59, 7/1998) further indicates that while animal models may be useful for determining the mechanism of a drug on smooth muscle cell proliferation, positive results should not be interpreted to mean that a given treatment will function in humans. "The extrapolation of animal studies directly to man is unreasonable given the vast differences between animal models and man, and the complexity of the restenotic process." See page 54, column 2, lines 3-12. In fact, the unpredictability in extrapolating results of such studies to humans was still noted in 1999 after the priority date of the instant application, when Johnson et al taught that small animal models "lacked efficacy in predicting the success of interventions to inhibit restenosis in humans", and found that small animal models fail to closely simulate human atherosclerosis and stenotic lesions. See abstract. Finally, Appleby and Kingston (Current Gene Therapy 4:153-182, 2004) reviewed the state of the art of restenosis gene therapy after the time of the invention. These authors relate that despite promising results from numerous animal studies, there has been a general failure to obtain similar results in humans. This is primarily due to an incomplete understanding of the vascular biology of restenosis which makes it difficult to select therapeutic genes, dissimilarity between humans and the animal models under study,

and difficulty in obtaining localized gene transfer into coronary arteries in vivo. The authors conclude that progress in each area will be required before gene therapy in the vasculature becomes a clinical reality. See abstract and last two paragraphs on page 176. For these reasons, the enabled use of the claimed invention is limited to the treatment of rabbits.

In summary, at the time of the invention, those of skill in the art recognized that one could not accurately extrapolate positive results from small animal models of smooth muscle cell proliferation to other animals, particularly humans; the specification fails to provide guidance that would allow such extrapolation; and the specification fails to provide any working example of treatment in any organism other than a rabbit. For these reasons, one of skill in the art could not practice the claimed methods commensurate in scope with the claims without undue experimentation.

Response to Arguments

Applicant's arguments filed 11/8/05 have been fully considered but they are not persuasive.

At page 2 of the response, Applicant addresses the predictability of treating intimal hyperplasia with VEGF-encoding nucleic acids. The Office has shown that Laitinen (1998) thought that although promising effects on cardiovascular diseases had been noted by adventitial delivery of genes in animal models using the collar device disclosed at page 16, lines 21-23 of the specification, further studies regarding gene transfer techniques, vectors, and safety of procedures are needed before a full

therapeutic potential of gene therapy in vascular diseases can be evaluated. Applicant states that the claims are directed to methods of treating or inhibiting intimal hyperplasia, not to treatment of vascular disorders in general, and asserts that "this aspect of the rejection has been obviated." This is unpersuasive because Applicant has not shown that inhibition of intimal hyperplasia with VEGF-encoding nucleic acids is more predictable than any other vascular disorder.

In the paragraph bridging pages 2 and 3 of the response, Applicant reiterates earlier arguments that the rabbit intimal hyperplasia model is an art-accepted animal model, relying for support on Strauss (202) and Farb (2001). Applicant asserts that animal models used for addressing issues of enablement do not have to provide perfect correlation with treatment in humans, and that there need only be a reasonable correlation. Applicant asserts that if the rabbit model was not a suitable model clinical researchers would not use it in their studies. This is unpersuasive because the Office has established that, around the time the invention was filed, no restenosis strategies based on inhibition of smooth muscle cell proliferation that successfully limited restenosis in animal models had ever been used to successfully treat intimal hyperplasia in humans. See Lafont (1995) above. As discussed in the rejection, this is because intimal hyperplasia in humans is a physiologically different process taking place in physiologically different structures than in the animal models such as the rabbit. The fact that animal models are used for research does not mean that the results obtained in these animal models will be applicable to humans, and the evidence of record shows that the results in animal models of hyperplasia both before and after the

time of the invention were not applicable to humans. With specific regard to whether or not there is a reasonable correlation between the small animal models and the human disease, the sentence bridging columns 1 and 2 on page 54, and column 52, lines 3-11 of Lafont (1995) is relevant. In this passage Lafont indicates that the usefulness of small animal models lays in providing answers to specific biochemical questions, e.g. determining the mechanism of action of a drug on smooth muscle cell proliferation, while noting that the results should not be interpreted to mean that the drug is also able to inhibit restenosis in man. Lafont concludes that "extrapolation of animal studies directly to man is ***unreasonable*** given the vast differences between animal models and man and the complexity of the restenotic process." Emphasis added. Thus the utility of animal models of intimal proliferation lies in answering specific biochemical questions, but those of skill in the art appreciate that there is not a reasonable correlation between these models and human disease that would support extrapolation of results from the models to humans.

At page 3 Applicant refers to data from a pig model, submitted in the Declaration of Dr. Martin filed 11/25/02, and states that this data was sufficient for the USFDA to approve Applicant's invention for testing in humans. Regarding the patentability of the instantly claimed invention, the declaration of Dr. Martin from 11/2/02 was unpersuasive for several reasons. The Declaration presents the results of an experiment in which nucleic acids encoding VEGF-D were delivered to the site of surgery in pigs which had undergone surgical anastomosis of the carotid artery and internal jugular vein. The Declaration provided no statistical analysis of the results, the sample size was small,

and the results indicated that the treatment may in fact increase intimal hyperplasia over time. See in particular, page 5, first sentence of paragraph 4 which indicates that at day 60 there was an increased degree of intimal proliferation/fibrosis and a reduction in luminal diameter in the groups which received VEGF-D adenovirus, when compared with the controls, and that luminal occlusion occurred only in animals treated with VEGF-D. Also, because intimal hyperplasia is known to occur in about 30% of arterial bypasses after two years (see specification at page 2, lines 10 and 11), it is not clear that an inhibition of intimal proliferation in 50% of individuals at 28 days after surgery is significant at all, particularly in view of the small sample size and the fact that after 60 days intimal proliferation and luminal occlusion increased in VEGF-treated individuals. In other words, if one would expect 70% of individuals to be unaffected by restenosis normally, it is not necessarily significant that intimal proliferation was inhibited in 50% of pigs. It must also be noted that the experiments set forth in the Declaration relied on VEGF-D, which was not available at the time the invention was filed. The discovery of VEGF-D was made public on 6/15/97 (Yamada et al Genomics 42(3): 483-488), well after the effective filing date of the instant application (11/1/96). The instant specification discloses only splicing alternatives isoforms of VEGF-A, originally called "VEGF". The specification as filed did not disclose VEGF-D, and it was not known to those of skill in the art at the time of the invention. The experiment described by Dr. Martin is not relevant to the issue of enablement of the claimed invention because the claimed invention does not embrace VEGF-D, so the Declaration of Dr. Martin is not persuasive regarding enablement of the claimed invention.

Applicant goes on to report at pages 3 and 4 positive results from a second round clinical trial, relying for support on a press release from Ark therapeutics. The effect on vascular graft patency in dialysis patients of periadventitially delivered adenovirus encoding VEGF-D was studied. All five patients that completed the study showed improved graft patency relative to previous graft access procedures. Graft patency was extended from a mean of 4.5 months to at least 14 months. These results are unpersuasive regarding enablement of the claimed invention because, similarly to the pig experiment discussed above, the clinical trial relied upon VEGF-D, a gene that was unknown at the time of the invention. As discussed above, the specification as filed disclosed only isoforms of VEGF-A, and did not disclose VEGF-D which is a different protein encoded by a different gene. As a result, the information contained in the press release is not persuasive regarding enablement of the claimed invention, and the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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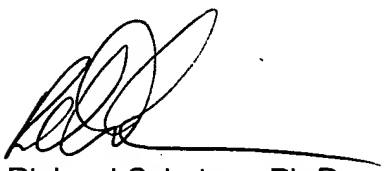

Richard Schnizer, Ph.D.